UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,301	02/17/2000	Joseph C. Glorioso	204001	7569

7590 06/05/2002

M Daniel Hefner
Leydig Voit & Mayer LTD
Two Presidential Plaza Suite 4900
180 North Stetson
Chicago, IL 60601-6780

EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 06/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/506,301	Applicant(s) GLORIOSO ET AL.	
	Examiner Gerald Leffers	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 3/11/02 as Paper No. 10, in which several changes were made to the claims. In Paper No. 10 claims were cancelled (claims 17-20), claims were amended (claims 1-2, 6, 8-9, 11) and new claims were added (claims 21-30). Claims 1-16 and 21-30 are pending in the instant application. A new rejection is made in this action that was not necessitated by amendment or by the IDS submitted 3/11/02. Therefore this action is not final.

Information Disclosure Statement

Receipt is acknowledged of an IDS, filed 3/11/02 as Paper No. 9. The signed and initialed PTO Form 1449 has been mailed along with this action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claimed invention is drawn towards a recombinant herpes simplex virus (HSV) comprising an adeno-associated virus (AAV) rep gene wherein the rep gene comprises a promoter controlling expression of a sequence encoding a rep polypeptide, and wherein either the promoter or the rep polypeptide is conditionally active. The rep protein can be rep78, rep68, rep62 or rep40. The promoter can be inducible or tissue-specific. The recombinant HSV can

comprise AAV ITR sequences flanking a non-AAV sequence. The HSV vector can be deficient in at least one essential HSV gene.

In the specification, the term HSV is described as encompassing any herpes simplex virus strain, but excluding "amplicons", where the HSV comprises an HSV origin of replication, an HSV-derived packaging sequence and sufficient machinery to permit the virus to replicate within permissive cells without the need for a helper HSV or plasmid sequences (e.g. page 4, lines 26-35). The specification teaches that the term "HSV" further encompasses strains having deletions in essential genes such that the HSV vector of the invention can only be replicated in permissive cells (e.g. pages 4-5, bridging paragraph). It is unclear from reading the specification as to at what point the number of mutations (e.g. deletions) of the HSV genome results in an "amplicon" as defined by the specification. For example, amplicons described in the references below could be replicated into HSV-1 virions by cells comprising complementing HSV-1 sequences integrated into the packaging cell genome. The issue is further clouded by the fact the implied definition of an amplicon as being a nucleic acid that does not comprise enough HSV machinery to permit the virus to replicate within permissive cells without the use of a helper virus or plasmid sequences appears to be contrary to the art. The art defines an "amplicon" as a term for any small, replicating DNA fragment (see the attached definition from the OneLook On-Line Medical Dictionary at http//www.onelook.conv). Read broadly, the claims thus encompass an HSV virus comprising an amplicon that possesses an HSV origin of replication, an HSV packaging sequence and an AAV rep gene under the control of a "conditionally active" promoter.

The specification describes a "conditionally active" rep protein or promoter as one that is "relatively more active under an identifiable permissive condition and relatively less under an identifiable nonpermissive condition". The terms "permissive" and "nonpermissive" conditions are not defined in the specification. A reasonably broad interpretation of the definitions provided by the specification might be that the term "conditionally active promoter" encompasses any promoter (e.g. the native rep promoter) that is inactive in a nonpermissive environment (e.g. in a virus outside of a cell) as opposed to a permissive environment (e.g. when in a suitable cell).

Claims 1-2, 5, 9, 12-13, 15-16, 21-24, 26-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Dong et al (reference AQ on Paper No. 4) (WO 95/06743; see the entire application).

Dong et al teach the construction of helper viruses for production of rAAV which comprise genes essential for AAV replication. Dong et al teach that the helper viruses of their invention can be derived from adenovirus or one of several different types of viruses classified in general as "herpesvirus", including HSV (page 6, lines 16-28). Dong et al teach that these helper viruses can either be replication competent (i.e. comprising viral packaging sequences and an origin of replication) or replication defective (page 15, lines 19-29). Dong et al specifically teach that the herpesviral helper viruses of their invention will comprise one or more of the AAV rep, lip and cap genes (page 7, lines 8-20). Dong et al teach that these genes can be inserted into the helper virus genome at positions where either essential or nonessential genes from the helper virus genome have been deleted (page 7, lines 21-32). The AAV rep, lip or cap genes can be under the control of either "natural" AAV promoters or heterologous promoters (e.g. the HSV tk

promoter). Dong et al teach that the choice of promoter is not critical so long as the promoter effectively directs expression of the AAV gene or genes, and that the promoter can be a constitutive promoter (e.g. page 8, lines 20-27; page 9, lines 4-14). Dong et al teach a prophetic example for insertion of AAV rep, lip and/or cap sequences into the genome of HSV featuring the HSV vector R7020. R7020 features deletion of approximately 700 bp from the domain of the thymidine kinase gene and all of the sequences from the 3' end of the IE63 (α27) gene to the α4 gene in the reiterated sequence of the S component of the HSV genome. The authors teach that the rep-lip-cap genes can be inserted into, at least, either of two positions including the site between the inserted tk gene and the HSV-2 DNA sequences and the site of the deletion of the natural tk gene (e.g. Example VI(1) page 44). The wildtype rep gene would be expected to produce each of the four rep proteins normally produced by AAV.

Claims 1-2, 5, 7-8, 12-16, 21-26 and 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Fraefel et al (reference BB on Paper No. 9) (Molecular Medicine, December 1997, Vol. 3, No. 12, pages 813-825; see the entire reference).

Fraefel et al teach the construction and use of HSV-1 viral stocks comprising an amplicon comprising the AAV rep gene under control of the HSV-1 IE 4/5 promoter and a reporter cassette flanked by two AAV ITRs (e.g. page 816, column 2, paragraph 1; Figure 1, pHYRGN; pages 819-820, bridging paragraph). Fraeful et al teach the HSV-1 IE 4/5 promoter was more effective (~ 10-fold) in promoting transduction of kidney and lung fibroblasts than hepatic cells (e.g. page 818).

Claims 1-2, 5, 9, 12-16, 21-24 and 27-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Conway et al (reference AZ on Paper No. 9) (Journal of Virology, Nov. 1997, Vol. 71, No. 11, pages 8780-8789; see the entire reference).

Conway et al teach the construction and use of HSV-1 viral stocks (e.g. HSV-RC/KOS or HSV-RC/d27) comprising an amplicon comprising the AAV-2 rep and cap genes under control of their own native promoters (p5, p19, p40) and an HSV origin of replication (oriS) (e.g. page 8781, column 1, last paragraph).

Claims 1-2, 5, 7-8, 12-16, 21-24 and 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnston et al (reference BE on Paper No. 9) (Human Gene Therapy, 10 February 1997, Vol. 8, pages 359-370; see the entire reference).

Johnston et al teach the construction and use of HSV/AAV hybrid viruses (e.g. the viral stocks described on page 362, columns 1-2) that comprise an "amplicon" comprising an HSV-1 origin of replication, HSV packaging signal and a lacZ reporter gene flanked by AAV inverted terminal repeat sequences (ITRs) (e.g. Abstract, Figure 2). At least one embodiment comprises the wildtype AAV rep gene under control of its own promoter to express each of the four AAV rep proteins (e.g. Figure 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dong et al (reference AQ on Paper No. 4) (WO 95/06743; see the entire application) in view of Glorioso et al (U.S. Patent No. 5,998,174; see the entire patent).

The teachings of Dong et al are described above and applied as before to claims 1-2, 5, 9, 12-13, 15-16, 21-24, 26-28; except:

Dong et al do not explicitly teach the alteration or deletion of the ICP27 gene for their HSV-1/AAV hybrid helper virus.

Glorioso et al teach the construction and use of a variety of HSV vectors (e.g. Abstract). Glorioso et al teach that the HSV genome is well characterized and that one can make deletion mutations in essential genes (in particular ICP4 & ICP27) such that the HSV vector is replication-defective unless grown in a host cell providing the missing translation product or products (column 2, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the recombinant HSV vector taught by Dong et al to include a deletion of at least part of the ICP27 gene because Dong et al teach that it is within the skill of the art to make the helper-virus constructs of their invention comprising deletions of any non-essential or essential gene (e.g. glycoprotein H or ICP27) so long as the essential gene products are provided in trans during replication of the helper virus and because Glorioso et al specifically teach that it is possible and desirable to make recombinant HSV vectors comprising a deletion of at least a portion of the ICP27 gene. One would have been motivated to do so in order to receive the expected benefit of limiting the induction of herpes viral replication during the methods taught by Dong et al for production of rAAV with the HSV-helper virus. Absent any evidence to the contrary, there would have been a reasonable expectation of success in incorporating a deletion in the ICP27 gene, as taught by Glorioso et al, in the recombinant HSV vectors taught by Dong et al for expression of AAV rep and cap during production of high-titer rAAV stocks.

Conclusion

Claims 1-16 and 21-30 are pending. Claims 1-2, 5, 7-9, 12-16, 21-29 are rejected. Claims 3-4, 6, 10-11 are objected to as being dependent upon a rejected claim. If rewritten in an independent form, claims 3-4, 6, 10-11 would be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

AA2
ggl
June 1, 2002

DAVID GUZO
PRIMARY EXAMINER